

Prikaz bolesnika | Case report

Hepatitis E Induced „Acute-On-Chronic” Liver Failure - Do We Transplant or Not?

„Acute-on-chronic” zatajenje jetre uzrokovano hepatitis E virusnom infekcijom - transplantirati ili ne?

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„acute-on-chronic”
transplantacija jetre***Abstract**

Hepatitis E virus is a pathogen of worldwide significance. In developed countries, foodborne transmission of zoonotic genotypes is the most common route of infection. Transfusion transmitted infection is also an important source of infection, particularly in immunocompromised population. In most cases, HEV infection is asymptomatic or presents as an acute self-limiting hepatitis. Rarely it leads to fulminant hepatitis or „acute-on-chronic” liver failure in people with pre-existing chronic liver diseases. The aim of this report is to present the first documented case of HEV-related „acute-on-chronic” liver failure in Croatia in a patient with chronic liver disease listed for liver transplantation. Due to increasing incidence in industrialised countries, HEV infection should always be considered in the differential diagnosis of acute hepatitis and in patients with unexplained worsening of chronic liver disease.

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Hepatitis E virusna (HEV) infekcija zarazna je bolest s rastućom stopom pojavnosti diljem svijeta. U razvijenim zemljama, najčešći put prijenosa zoonotskih genotipova HEV virusa je putem hrane, dok prijenos putem krvnih derivata predstavlja važan izvor infekcije u imunokompromitiranim populacijama. U većini slučajeva, HEV infekcija je asimptomatska ili se uglavnom prezentira u obliku akutnog samolimitirajućeg hepatitisa, rijetko dovodeći do fulminantnog hepatitisa ili „acute-on-chronic” zatajenja jetre kod osoba s pre-egzistentnim bolestima jetre. Cilj ovog rada je prikazati prvi dokumentirani slučaj „acute-on-chronic” zatajenja jetre izazvanog HEV-om u Hrvatskoj kod bolesnika s kroničnom bolesti jetre koji je bio uvršten na listu za transplantaciju jetre. Zbog povećane učestalosti u razvijenim zemljama, HEV infekciju treba uvijek razmotriti u diferencijalnoj dijagnozi akutnog hepatitisa i kod bolesnika s nejasnim pogoršanjem kronične bolesti jetre.

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Introduction

Hepatitis E has a substantial impact on human health affecting 3 million patients and causing 70,000 deaths annually worldwide^[1]. In developed countries, the most common route of infection is foodborne transmission of zoonotic genotypes (G 3 and 4) caused by consumption of raw and undercooked meat, and transfusion, which is important source of infection in immunocompromised population^[2].

In most cases, HEV infection is asymptomatic or presents as an acute self-limiting hepatitis, rarely leading to fulminant hepatitis or „acute-on-chronic” liver

failure (ACLF) in people with pre-existing chronic liver diseases (CLD)^[3].

In the European general population HEV seroprevalence rate ranges from 0.6% to 86.4% with the highest prevalence reported in Arie`ge in France, while the incidence of an acute infection ranges from 0.2% to 3.2%^[4]. However, the data on impact of acute HEV infection on the prognosis and survival of pre-existing CLD patients in Europe is limited^[6-9].

We report the first documented case of HEV induced ACLF in Croatia in a patient with previously undiagnosed chronic liver disease.

Case report

A 67-year-old man with one-week history of fever and diarrhoea was admitted to the hospital. He had unremarkable medical history except for asymptomatic cholelithiasis and arrhythmia under good control with atenolol. He denied taking any drugs or herbal medicine, and he drank no more than two glasses of wine per day. A month before the onset of his symptoms, he travelled to Sicily.

After admission, his liver function rapidly deteriorated with worsening liver function tests, as indicated by rising bilirubin (total bilirubin 130 $\mu\text{mol/L}$), elevated transaminases (AST 3010 U/L, ALT 4000 U/L) and worsening coagulopathy (INR 3.1). Infectious work up was negative for hepatitis A, B, C, human immunodeficiency virus, cytomegalovirus, and herpes simplex virus and positive for previous EBV infection. Blood, urine and bacterial stool culture were negative as were *Clostridium difficile* antigen and toxins in stool. Dengue virus, enteroviruses, leptospirosis, adenoviruses and *Coxiella burnetii*, as well as autoimmune liver panel (antinuclear antibody, anti-smooth muscle antibody and anti-LKM) all tested negative.

Due to progressive deterioration of liver function the patient was urgently transferred to the Liver Transplant Centre. Abdominal ultrasound showed enlarged liver without focal lesions, normal bile ducts and normal hepatic blood vessels. Liver biopsy revealed acute hepatitis of unknown aetiology, nonspecific chronic inflammation without severe necrosis but with marked microvesicular steatosis (with foaming of hepatocytes). The patient was transferred from the medical ward into the Intensive care unit (ICU) due to deterioration. Over the next few days he developed hepatic encephalopathy (grade III to IV) and required invasive mechanical ventilation. The Multislice Computed Tomography scan of the head excluded pathological intracranial processes and he was listed for liver transplantation with MELD score of 34.

His anti-HEV IgM and IgG resulted positive and the antiviral treatment with ribavirin (8mg/kg) was started, pending PCR analysis results. Since PCR HEV RNA resulted negative six days into treatment, ribavirin was discontinued. Management of critically ill patient consisted of respiratory support, parenteral antibiotics (cefuroxime and metronidazole), L-ornithine-L-aspartate, intensive insulin therapy, mechanical and pharmacological thromboprophylaxis, stress ulcer prophylaxis and enteral feeding. Intensive care therapy and supportive treatment resulted in the improvement of the liver function (AST 185 U/L; ALT 361 U/L, total bilirubin 127 $\mu\text{mol/L}$, INR 1.6, V factor 0.7%). Three months after discharge from the hospital, the patient

was well, without signs of liver disease and his liver function tests were normal. Furthermore, non-invasive evaluation of liver fibrosis was performed by implementing transient elastography with a median liver stiffness of 7.5 kPa indicating stage F2 fibrosis. Finally, he was removed from the liver transplant waiting list.

Discussion

This is the first documented case of HEV induced ACLF in Croatia, with severe clinical course which made him a candidate for liver transplantation. The vast majority of patients with HEV infection have favourable outcome and they rarely present with symptoms of acute hepatitis or with extrahepatic manifestations^[5]. In contrast to several reports of HEV genotype 1 and 2 induced ACLF in Asia and Africa, the burden and prognosis of HEV genotypes 3 and 4 in developed countries is unknown. Available data indicate that some cases of severe liver injury with adverse outcome among CLD patients in Europe is related to autochthonous hepatitis E.

The first documented report of liver decompensation in cirrhotic patients with fatal outcome due to HEV infection was published in UK in 2007 by Dalton et al.^[6]. Another study published in the same year in France described seven patients with fulminant liver failure due to HEV genotype 3 infection^[7]. Six of them had CLD. Data from Switzerland reported severe clinical course in two patients with CLD and symptomatic acute HEV with fatal outcome^[8]. However, a more recent large-scale study from the UK and France by Blasco-Perrin et al. found only minor (3,2%), predominantly in south-west France, number of HEV cases among 343 patients with decompensated CLD indicating it is an uncommon cause of liver decompensation. Moreover, mortality was estimated to be 27% and was not significantly different compared to patients without hepatitis E infection^[9]. The incidence of HEV as a cause of decompensation in CLD patients considerably varies geographically and probably also changes over time, as a reflection of the amount of circulating virus in a given population at a given time.

In the presented case, risk factors for acute deterioration of liver function were male gender, age and underlying chronic liver disease considering liver histology which has shown nonspecific chronic inflammation with marked microvesicular steatosis (with foaming of hepatocytes) and FibroScan measurement indicating stage F2 fibrosis. Given the patient's medical data about his drinking habits and limited interpretation of histology in the setting of aetiology of underlying liver disease, it is very difficult to distinguish NAFLD from alcohol related CLD. In terms of making preliminary

diagnosis, markedly elevated liver enzymes strongly suggest the diagnosis to the clinician even prior obtained HEV results. However, in some cases with the same clinical presentation, the ALT value may only be modestly elevated (<300) suggesting the diagnosis of hepatitis E in patients with decompensated CLD is not straightforward^[9]. Moreover, considered to be mostly a disease of developing countries, HEV infection is still rarely considered in the differential diagnosis of acute liver failure in European countries. Drug induced liver injury (DILI) represents a mayor diagnostic dilemma when distinguishing HEV infection^[3]. Another diagnostic difficulty is the differentiation between autoimmune hepatitis or Epstein-Barr virus infection and HEV infection since both conditions can produce false positive HEV serology results^[3]. Therefore, every patient with symptoms consistent with acute hepatitis or unexplained worsening of CLD should be tested both with PCR and serology. A negative PCR does not exclude acute HEV infection^[3].

The patient was listed for liver transplantation due to rapid worsening of clinical condition with overt encephalopathy and significant coagulopathy. Management of our patient consisted of supportive treatment which led to improvement of his liver function. In this case, the use of ribavirin did not have effect on the favourable outcome. The reason for this was that the patient was PCR negative at the time of enrolling ribavirin, indicating he had already achieved spontaneous viral clearance. However, we did not observe any adverse effects of treatment with ribavirin. The efficacy and safety of ribavirin in patients with chronic HEV infection was proven to be beneficial, however the data for patients with serious liver disease is scarce and needs prospective evaluation in larger population studies^[10].

In conclusion, since HEV infection could be associated with significant morbidity and mortality, it is crucial to perform testing in all patients with symptoms consistent with acute hepatitis and patients with unexplained flares of chronic liver disease. Higher awareness of HEV in a differential diagnosis could reduce the number of cases of cryptogenic liver injury.

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